NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND ARTHRITIS ADVISORY COMMITTEE

JULY 20, 1999

NDA 21070 FLEXERIL OTC SWITCH

ABUSE POTENTIAL REVIEW

REVIEW AND EVALUATION OF DRUG ABUSE DATA
Consultative Review

Division of Anesthetic, Critical Care & Addiction Drug Products (HFD-170)

NDA: 21-070

Sponsor: **MERCK & Co., Inc.**
West Point, PA

Drug: Nonprescription FLEXERIL™ MR, 5 mg Tablets
(Cyclobenzaprine hydrochloride)

Indication: Treatment for back and neck muscle spasm

Date of Submission: January 29, 1999 and March 23, 1999

Reviewed by: Michael Klein, Ph.D. (Team Leader)
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Date of Review: June 3, 1999

The sponsor submitted drug abuse and overdose data in support of its new drug application that concerns the change of Flexeril™ (cyclobenzaprine hydrochloride) from a prescription to an over-the-counter drug. The sponsor provided information for review that concerned:

1. The Drug Abuse Warning Network (DAWN).
2. Poison Control Center Reports of overdosage, misuse and abuse, from the American Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System (TESS).
3. Adverse events reports of abuse and overdosage.
4. A description of a possible withdrawal syndrome resulting from extended use of cyclobenzaprine.

In addition to review of the above, review of the open scientific literature concerning abuse potential and the FDA Adverse Events Reporting System (AERS) and 1997 DAWN emergency department and medical examiner data was conducted.

Preclinical Evaluation. Cyclobenzaprine, 3-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-N,N-dimethyl-1-propamine hydrochloride, is a muscle relaxant that is pharmacologically and structurally similar to the tricyclic antidepressants. Some of the currently available muscle relaxants have been abused for their psychoactive effects and their abuse potential has been characterized in preclinical and/or clinical abuse liability studies. Review of the

preclinical literature has revealed that the abuse potential of cyclobenzaprine (Flexeril™) has not been evaluated.

There are several preclinical behavioral studies that are routinely performed to characterize the abuse potential of a compound. The drug discrimination paradigm is routinely used in the preclinical assessment of the abuse potential of a drug and it is widely accepted as an animal model for human subjective effects. There is a wealth of preclinical data to support the general statement that for many drugs their subjective effects in humans and their discriminative stimulus properties in animals (e.g. LSD-like, amphetamine-like, narcotic-like) parallel one another (Schuster and Balster, 1977; Glennon and Rosecrans, 1981; Chait, *et al.*, 1984; Griffiths *et al.*, 1985). In this paradigm, the animal is required to discriminate between a drug state and a non-drug state. Within the operant chamber, the animal is trained to elicit a response on one lever (e.g. right) following drug injection and on the opposite lever (left) following vehicle injection. Once the animal has learned to respond on the correct lever based on the interoceptive cues, novel drugs can be evaluated in order to determine whether or not they elicit similar stimulus properties. Drugs that elicit similar subjective effects in humans are considered likely to produce similar discriminative stimulus effects in animals.

The ability to function as a "positive reinforcer" (i.e., reinforcing efficacy) is another characteristic of all dependence-producing drugs. It is generally accepted in the scientific community that the ability of addictive drugs to serve as "positive reinforcer" is the core property that promotes the development and maintenance of addiction (Thompson and Schuster, 1968; Thompson and Unna, 1977; Balster, 1991). The self-administration paradigm is widely used to determine whether or not a drug can control behavior, that is, function as a positive reinforcer and to evaluate the abuse potential of the drug. The self-administration procedures using nonhuman primates and rats have been shown to be a valid and reliable predictor of the potential of a compound to result in drug dependence (i.e., addiction). In this paradigm, the animals are trained to self-administer a known drug of abuse (e.g. cocaine). Once stable responding is maintained, test drugs are substituted for the training drug to determine if they will maintain responding to the new drug. The self-administration paradigm has been valuable in evaluating the reinforcing efficacy of opioids, CNS depressants, cocaine, amphetamine and phencyclidine-like drugs. Preclinical studies have shown that there is a strong concordance between the types of drugs that serve as reinforcers in animals and the many illicit drugs associated with problems of addiction, dependence or abuse by man (Johanson and Balster, 1978; Griffiths *et al.*, 1980; Johanson and Schuster, 1981; Johanson *et al.*, 1987; Woolverton and Nader, 1990).

In addition to the primary reinforcing effects contributing to the dependence producing potential of a drug, other factors also can profoundly affect the drug pattern of use and the likelihood that the drug use will be continued. Among these factors are the capacities of some drugs to produce tolerance and/or physical dependence. Tolerance develops when, after repeated administration, a given dose of a drug produces a decreased effect resulting in increasing larger doses being administered in order to obtain the desired

effect. Physical dependence refers to an altered physiological state resulting from the repeated administration of a drug, which necessitates the continued use of the drug in order to prevent the appearance of the withdrawal syndrome characteristics for the particular drug if the drug is discontinued.

The propensity to cause physical dependence can be examined in animal studies. There are three types of animal models for assessing the drug ability to induce physical dependence. The first study is called the substitution study. In this model, a single dose of the test drug will be substituted in animals (rats or primates) that have been made physically dependent on a drug (i.e., an opiate or a barbiturate) known to produce physical dependence. The drug is substituted when the animal is beginning to show signs of withdrawal. The second model is known as precipitated withdrawal study. In this assay, the ability of the drug to precipitate withdrawal in opiate- or barbiturate-dependent animals is evaluated. The third animal study is known as the primary dependence test. In this assay, drug-naive animals are given repeated administration of the test drug for periods of a few weeks to a few months. The dependence potential of the test drug can be evaluated by administering an antagonist and/or by abrupt cessation of the drug. The animals are observed for physical signs and symptoms of withdrawal.

Drug Abuse Warning Network (DAWN). The DAWN Emergency Department (ED) data comes from a representative sample of hospital emergency departments which are weighted to produce national estimates (**Table 1**). The tables below show the estimated number of mentions for cyclobenzaprine and comparator drugs, carisoprodol and diazepam, arranged by age, gender and motive for taking the drug (**Tables 3, 4, 5**). Since one variable "Motive" applies to the entire episode and since more than one drug per episode may be mentioned, the "Motive" may not apply to the specific sole drug under review, but to the effects of the drug combination.

Carisoprodol and diazepam were chosen as comparator drugs because of their therapeutic application and pharmacological activity as central depressants. Diazepam is indicated for the management of anxiety disorders, for the short term relief of symptoms of anxiety and for its muscle relaxant properties. Carisoprodol is indicated as an adjunct to rest, physical therapy and the relief of discomfort associated with acute, painful musculoskeletal conditions. Of the three drug substances, diazepam is the sole agent that is a controlled substance and its manufacture and distribution are subject to the controls imposed to Schedule IV substances under the Controlled Substances Act.

The Medical Examiner (ME) data does not come from a representative sample of medical examiner offices and cannot be used to produce national estimates of the number of drug-related deaths. Because some ME's stop sending data and others are continuously being recruited into the system, the number of contributing ME's changes from year to year. For the purpose of producing trend data, a consistent panel of ME's has been established which has been reporting to DAWN consistently (at least 10 months of each year in question) over the time period of interest.

Table 1. Weighted Emergency Department Mentions for 1992-1997 of CYCLOBENZAPRINE, CARISOPRODOL and DIAZEPAM.

DRUGS	1992	1993	1994	1995	1996	1997
Cyclobenzaprine	2,731	2,647	3,130	2,924	3,599	3,626
Carisoprodol	5,922	6,570	6,571	7,771	7,279	6,133
Diazepam	13,947	12,409	13,568	14,248	13,601	13,367

Table 2, immediately below, contains data from the National Prescription Audit Plus, IMS Health and are the total numbers of prescriptions (new and refill) dispensed by US retail pharmacies (chain, independent and food stores). The data from 1995 to 1998, in addition to the prescriptions dispensed by US retail pharmacies, includes mail orders.

Table 2. IMS Drug Utilization Data Reported as Annual Prescription Sales in the U.S.A. for CYCLOBENZAPRINE, CARISOPRODOL and DIAZEPAM.

Drug	Projected Total Prescriptions (000) [a]						
	1992	1993	1994	1995	1996	1997	1998
Cyclobenzaprine	7,347	7,682	8,172	8,556	9,153	9,574	10,459
Carisoprodol	5,126	5,888	6,334	6,823	7,514	8,058	8,615
Diazepam[b]	13,031	12,657	12,228	12,158	11,971	11,551	11,736

[a] Source: IMS America NPA + TCR, On-line. The 1992-1994 period includes projected total prescriptions dispensed by US retail pharmacies (chain, independent and food stores). The 1995-1998 period includes projected total prescriptions dispensed by US retail pharmacies and mail orders in the US. Not for use outside FDA without prior clearance by IMS America [b] Schedule IV Controlled Substance

The frequency of emergency department mentions relative to the total number of prescriptions for 1992-1997 for cyclobenzaprine is of the order of approximately 4 mentions per ten thousand prescriptions. For the same period of time, the frequency of emergency department mentions per ten thousand prescriptions is approximately 10 for carisoprodol and 11 for diazepam. It is noted that carisoprodol and diazepam have a comparable frequency of reporting that is higher than that of cyclobenzaprine.

The Drug Abuse Warning Network (DAWN) shows a steady number of emergency room estimated mentions since 1992 to 1997 (Table 1). For cyclobenzaprine, most of the reports involved females (56%). Forty-two percent of the carisoprodol mentions involved individuals over 35 years of age, followed by 33 % in the age group of 26-34; 19% in the age group of 18-25 and 6.5% in the 6-17 age group. The motivation for taking cyclobenzaprine was primarily associated with suicide (68%), other psychic

effects (10%), unknown (9%), dependence (9%) and recreational use (0.3%). In 84% of the carisoprodol-related mentions, overdose was the reason for the emergency visit, unknown/ other and no response (11%), followed by seeking detoxification (1.7%), accident (2%) and unexpected reaction (6%). Cyclobenzaprine reports of abuse were mainly related to combinations with alcohol. Carisoprodol and diazepam were mainly taken in combination with alcohol, amphetamine, cocaine, marijuana, hydromorphone, heroin, hydrocodone and other opiates (**Table 6**).

Table 3. Weighted Emergency Department CYCLOBENZAPRINE Mentions, by Age Group, Gender and Motive for Taking the Substance. Values expressed as percentage in parenthesis ( ) of the total number of mentions for the drug in the specified year.

	1992	1993	1994	1995	1996	1997
Total	2,731	2,647	3,131	2,924	3,599	3,626
Age Group						
6-17	310 (11%)	230 (9%)	335 (11%)	183 (6%)	133 (4%)	234 (6.5%)
18-25	848 (31%)	729 (28%)	928 (30%)	757 (26%)	615 (17%)	703 (19%)
26-34	693 (25%)	857 (32%)	704 (22%)	1,017 (35%)	1,115(31%)	1,182(33%)
35+	880 (32%)	831 (31%)	1164 (37%)	967 (33%)	1,735(48%)	1,506(42%)
Unknown	.....	.....	.....	.....	.....	.....
Gender						
Male	1,184 (43%)	905(34%)	1,254(40%)	1,175 (40%)	1,362(38%)	1,545(43%)
Female	1,483 (54%)	1,682(64%)	1,868(60%)	1,746 (60%)	2,039(57%)	2,019(56%)
Unknown	65 (2%)	61 (2%)	9 (0.3%)	.....	197 (5.5%)	62 (1.7%)
Reason for Visit						
Unexpected Reaction	27 (1%)	74 (3%)	36 (1%)	81 (3%)	21 (0.6%)	22 (0.6%)
Overdose	2,534 (93%)	2,403 (91%)	2,597(83%)	2,759 (94%)	3,104(86%)	3,053(84%)
Withdrawal	2 (0.1%)	.....	9 (0.3%)	.....	72 (2%)	.....
Chronic Effects	5 (0.2%)	.....	(0.2%)	.....	.....	.....
Oth/Unk/ No Resp	152 (6%)	158 (6%)	391(13%)	66 (2%)	236 (6.5%)	414 (11%)
Seeking Detox	10 (0.4%)	8 (0.3%)	79 (2.5%)	.....	142 (4%)	63 (1.7%)
Accident/ Injury	1 (0.04%)	5 (0.2%)	12 (0.4%)	.....	16 (0.4%)	71 (2%)
Motive for Taking the Drug						
Dependence	19 (0.7%)	37 (1.4%)	166 (5%)	15 (0.5%)	105(3%)	316 (9%)
Suicide	2,179 (80%)	2,120 (80%)	2,238 (71.5%)	2,496 (85%)	2,293 (64%)	2,479 (68%)
Oth/Unk/ No Resp	235 (9%)	199 (7.5%)	400 (13%)	250 (8.5%)	500 (14%)	344 (9%)
Recreational Use	8 (0.3%)	16 (0.6%)	24 (0.8%)	14 (0.5%)	74 (2%)	120 (0.3%)
Other Psych. Effect	291 (11%)	276 (10%)	303 (10%)	149 (5%)	626 (17%)	366 (10%)

..... Estimated quantity less than 10 or zero. Source: Office of Applied Studies, SAMHSA, DAWN.

Table 4. Weighted Emergency Department CARISOPRODOL Mentions, by Age Group, Gender and Motive for Taking the Substance. Values expressed as percentage in parenthesis ( ) of the total number of mentions for the drug in the specified year.

	1992	1993	1994	1995	1996	1997
Total	5921	6570	6571	7,771	7,279	6,133
Age Group						
6-17	227 (3.8%)	379(6%)	421(6%)	470 (6%)	235 (3%)	443 (7%)
18-25	848 (14%)	984(15%)	882(13%)	1,383(18%)	1,106 (15%)	667 (11%)
26-34	2224 (38%)	1868(28%)	2047(31%)	2,181(28%)	1,686 (23%)	1,689 (28%)
35+	2621 (44%)	3338(51%)	3222(49%)	3,733(48%)	4,252 (58%)	3,275 (53%)
Unknown	.....	.....	.....	.....	.....	69 (1%)
Gender						
Male	2192 (37%)	2069 (31%)	2819 (43%)	2,805 (36%)	2,695 (37%)	2,416 (39%)
Female	3710 (63%)	4413 (67%)	3593 (55%)	4,884 (63%)	4,486 (62%)	3,651 (60%)
Unknown	19 (0.3%)	88 (1%)	159 (2%)	83 (1%)	99 (1%)	66 (1%)
Reason for ER Visit						
Unexpected Reaction	132 (2%)	249 (4%)	153 (2%)	268 (3%)	448 (6%)	425 (7%)
Overdose	4991 (84%)	5272 (80%)	5463 (83%)	6,529 (84%)	6,049 (83%)	4,399 (72%)
Withdrawal	9 (0.1%)	54 (0.8%)	17 (0.3%)	136 (2%)	142 (2%)	70 (1%)
Chronic Effects	14 (0.2%)	36 (0.5%)	21 (0.3%)	18 (0.2%)	15 (0.2%)	82 (1%)
Oth/Unk/No Resp	313 (5%)	572 (9%)	614 (9%)	376 (5%)	382 (5%)	543 (9%)
Seeking Detox	247 (4%)	238 (4%)	218 (3%)	274 (3.5%)	223 (3%)	353 (6%)
Accident/Injury	215 (4%)	149 (2%)	85 (1%)	170 (2%)	20 (0.3%)	263 (4%)
Motive for Taking the Drug						
Dependence	655 (11%)	758 (11)	422 (6%)	782 (10%)	664 (9%)	786 (13%)
Suicide	3044 (51%)	3934 (60%)	3830 (58%)	4,150 (53%)	4,010 (55%)	2,781 (45%)
Oth/Unk/No Resp	903 (15%)	430 (7%)	1193 (18%)	1,211 (16%)	996 (14%)	1 134 (18%)
Recreational Use	269 (4.5%)	292 (4%)	330 (5%)	299 (4%)	426 (6%)	413 (7%)
Oth Psych Effect	1051 (18%)	1156 (18%)	796 (12%)	1,330 (17%)	1,182 (16%)	1,020 (17%)

..... Estimated quantity less than 10. Source: Office of Applied Studies, SAMHSA, DAWN.

Table 5. Weighted Emergency Department DIAZEPAM Mentions, by Age Group, Gender and Motive for Taking the Substance. Values expressed as percentage in parenthesis ( ) of the total number of mentions for the drug in the specified year.

	1992	1993	1994	1995	1996	1997
Total	13,947	12,409	13,568	14,248	13,601	13,367
Age Group						
6-17	384 (3%)	498 (4%)	442 (3%)	578 (4%)	600 (4%)	696 (5%)
18-25	1,738 (12%)	1,736 (14%)	2,064 (15%)	1,976 (14%)	1,869 (14%)	2,298 (17%)
26-34	5,077 (36%)	4,303 (35%)	4,280 (32%)	3,519 (25%)	3,840 (28%)	2,981 (22%)
35+	6,744 (48%)	5,872 (47%)	6,781 (50%)	8,158 (57%)	7,286 (54%)	7,386 (55%)
Unknown	.....	.....	.....	17(0.1)	.....	.....
Gender						
Male	6,163 (44%)	5,012 (40%)	6,006 0.5%)	5,687 (40%)	6,137 (45%)	5,700 (43%)
Female	7,622 (55%)	7,134 (57%)	7,448 (55%)	8,513 (60%)	7,302 (54%)	7,644 (57%)
Unknown	159 (1)	261 (2)	113(0.8)	48 (0.3)	163 (1)	22 (0.2)
Reason for ER Visit						
Unexpect. Reaction	702 (5%)	629 (5%)	570 (4%)	602 (4%)	839 6%)	742 (5.5%)
Overdose	10,189 (73%)	8,824 (71%)	9,963 (73%)	11,311 (79%)	9,307 (68%)	9,657 (72%)
Withdrawal	430 (3%)	547 (4%)	511 (4%)	393 (3%)	405 (3%)	228 (1.7%)
Chronic Effects	285 (2%)	233 (2%)	242 (2%)	307 (2%)	214 (1.6%)	236 (1.8%)
Oth/Unk/No Resp	898 (6%)	899 (7%)	934 (7%)	639 (4%)	1,484 (11%)	1,151 (9%)
Seeking Detox	1,224 (9%)	947 (8%)	1,099 (8%)	836 (6%)	1,122 (8%)	1,110 (8%)
Accident/Injury	215 (1.5%)	328 (3%)	248 (2%)	160 (1%)	230 (1.7%)	243 (1.8%)
Motive for Taking the Drug						
Dependence	2265 (16%)	2407 (19%)	2640 (19%)	2,076 (15%)	2,918 (21%)	2,496 (19%)
Suicide	7904 (57%)	6786 (55%)	7819 (58%)	8,997 (63%)	6,821 (50%)	7,591 (57%)
Oth/Unk/ No Resp	1262 (9%)	1253 (10%)	1235 (9%)	1,279 (9%)	1,328 (10%)	1,283 (10%)
Recreational use	839 (6%)	668 (5%)	543 (4%)	877 (6%)	1,013 (7%)	701 (5%)
Oth Psych effect	1678 (12%)	1295 (10%)	1332 (10%)	1,020 (7%)	1,521 (11%)	1,295 (10%)

..... Estimated quantity less than 10 Source: Office of Applied Studies, SAMHSA DAWN

Table 6. Drugs of Abuse, including Alcohol, Used in Combination with CYCLOBENZAPRINE CARISOPRODOL and DIAZEPAM (ED Mentions).

Substance in Combination	1995	1996	1997
CYCLOBENZAPRINE			
Alcohol in Combination	1,064	1,628	968
Amphetamine	64	.....	.....
Cocaine	.....	.....	192
"Crack" Cocaine	.....	.....	59
Heroin	.....	.....	67
Hydrocodone	.....	.....	12
Hydromorphone	64	.....	.....
Marijuana	78	19	.....
Methamphetamine	.....	.....	58
Oxycodone	11	.....	.....
CARISOPRODOL			
Alcohol in Combination	2,319	2,165	1,783
Amphetamine	13	102	18
Cannabinoids	.....	14	123
Cocaine	86	237	374
Cocaine 8-Ball	.....	63	.....
Crack	136	14	67
Hydromorphone	13	.....	.....
Heroin	99	34	58
Hydrocodone	203	211	16
Marijuana/Pot	291	32	177
Methadone	.....	.....	19
Methamphetamine	11	.....	.....
Opiates	34	43	18
THC	79	.....	127
DIAZEPAM			
Alcohol in combination	6,175	6,623	5,634
Amphetamine	119	92	97
Cannabinoids	48	30	241
Cocaine	1,122	1,630	1,226
Codeine	98	90	36
Crack	224	146	337
Heroin	633	873	923
Hydrocodone	77	204	16
Hydromorphone	64	.....	.....
Ketamine	.....	.....	59
LSD	16	.....	.....
Marijuana	188	749	528
Methadone	136	128	59
Methamphetamine	70	22	147
Morphine	22	88	12
Opiates	199	65	58
PCP	25	13	15
Pot	11	128	228
Quaalude	72	.....	.....
Speed	78	.....	.....
THC	19	82	24

The number of deaths associated with cyclobenzaprine for 1992-1997 has remained steady and low compared to carisoprodol and diazepam. See **Table 7** below. The frequency of reported ME's relative to the number of prescriptions (from IMS America) for the three drugs shows that the ME reporting rate for diazepam is approximately 19 times greater and approximately 4 times greater for carisoprodol than for cyclobenzaprine. For the period 1992-1997, there were 135 ME's per 50,484,000 prescriptions for cyclobenzaprine, 418 ME's per 39,743,000 prescriptions for carisoprodol, and 3,728 ME's per 73.596,000 prescriptions for diazepam.

Table 7. Medical Examiner Data for CYCLOBENZAPRINE, CARISOPRODOL and DIAZEPAM, consistent panel (1992-1997).

Drug	1992 Total	1993 Total	1994 Total	1995 Total	1996 Total	1997 Total
Cyclobenzaprine	11	19	23	24	23	35
Carisoprodol	54	51	63	72	73	105
Diazepam	601	545	587	620	674	701

Table 8 shows other drugs associated with the deaths reported for cyclobenzaprine, carisoprodol and diazepam. Other drugs of abuse such as cocaine, amphetamine, marijuana, heroin, phencyclidine (PCP), ketamine and opioids are mentioned in several of the death reports that involved carisoprodol and diazepam

Table 8. Medical Examiner Mentions for Alcohol and Other Drugs of Abuse Taken in Combination with CYCLOBENZAPRINE, CARISOPRODOL and DIAZEPAM, Consistent Panel, for 1992-1997.

CYCLOBENZAPRINE						
Other Substances	**1992**	**1993**	**1994**	**1995**	**1996**	**1997**
Alcohol in comb.	1	7	4	8	6	7
Cocaine	.	2	6	5	3	9
Marijuana/Hashish	.	.	.	2	1	2
Heroin/Morphine	.	5	6	5	6	9
Methadone	.	2	.	1	2	1
Hydrocodone	2	1	1	.	2	3
Codeine	2	2	3	.	1	4
Oxycodone	1	2	.	1	2	4
CARISOPRODOL						
Alcohol in comb.	12	10	9	18	14	17
Cocaine	9	4	6	10	5	16
Amphetamine	.	.	2	1	3	4
Methamphetamine	.	2	4	1	1	4

Marijuana/Hashish	.	1	1	2	1	3
Heroin/Morphine	15	15	8	22	15	33
Methadone	3	3	2	3	6	3
Oxymorphone	1	.	1	.	1	.
Hydromorphone	.	.	.	1	.	4
Hydrocodone	8	12	9	14	17	32
Codeine	12	12	13	17	16	21
DIAZEPAM						
Alcohol in comb.	173	176	182	188	198	200
Cocaine	185	153	192	198	192	216
Amphetamine	14	10	9	14	11	14
Methamphet/Speed	22	22	26	19	19	32
Marijuana/Hashish	19	29	47	45	51	44
LSD	.	.	1	.	.	.
PCP/ PCP comb.	7	8	8	9	1	8
Heroin/morphine	249	232	247	266	302	310
Methadone	58	57	46	64	73	63
Oxymorphone	2	3	4	5	.	.
Hydromorphone	2	2	5	2	3	4
Hydrocodone	22	20	28	35	42	59
Ketamine	1	.	.	1	.	2
Codeine	142	94	102	102	140	133
Fentanyl	7	1	2	2	5	2
Oxycodone	11	13	10	15	8	20

Adverse Event Reporting System (AERS). For each drug, AERS was searched for all terms indicating Drug Abuse, Drug Dependence or Drug Withdrawal. Overdose terms were not included.

There are some limitations to counts of AERS cases, such as:

1. AERS is a spontaneous, voluntary reporting database with all reports required to have a drug and an adverse event; therefore, all reports are retrospective.
2. Although AERS links follow-up reports into the same "case" there may be duplicate reports counted as a separate case.
3. It is known that there is underreporting of most adverse events although the extent of underreporting is unknown.

4. No assessment of causality has been made other than the association made by the reporter of the event.
5. There are various factors affecting voluntary reporting of adverse drug events such as the calendar year, the amount of time from first marketing the drug, severity of the event, association of the event to the drug, media attention, and health professional notices.
6. The method of coding the adverse events (or reactions) changed in November 1997 from a simpler system with fewer, more broad, coding terms to a more complex system with a far greater number of more specific coding terms and a more complicated method of categorization. Each of the older report's reaction codes were recorded to a single code in AERS but the actual event recorded in the report may have a better, more specific, reaction code in AERS. Without reviewing the images of each of these old reports, the specific adverse event(s) may not be coded as accurately in AERS as is possible with the AERS coding system.
7. Since adverse events are underreported, counts of cases in AERS cannot be used to determine incidence rates. Reporting rates may be calculated but trending of reporting rates and comparison of reporting rates among drugs should be undertaken with caution knowing the above limitations and whatever additional limitations attributed to the particular drug(s) or adverse event (s).

In spite of these limitations, AERS reports have been found to be very important in identifying significant signals of drug associated adverse events.

AERS was searched for terms indicative of ***Drug Abuse***, ***Drug Dependence*** or ***Drug Withdrawal***, but not including ***Overdose*** terms. **Table 9** shows AERS counts of cases for the drug. The sponsor has stated that because of pharmacologic similarities of cyclobenzaprine to the tricyclic drugs, withdrawal symptoms may be possible, though they have not been reported. Also, in the NDA is the statement that abrupt cessation of treatment after prolonged administration may lead to nausea, headache, and malaise, but that these events are not indicative of addiction.

Table 9. AERS Counts of Cases by Drug (Terms searched: Drug Abuse, Drug Dependence and Drug Withdrawal).

AERS COUNTS OF CASES BY DRUG		
Drug (Approval date)	***Trade Name***	***Total Cases***
Cyclobenzaprine (August 1977)	Flexeril	12
Carisoprodol (April 1959)	Soma	59
Diazepam (November 1963)	Valium	289

Review of the 12 cyclobenzaprine reports that are associated with the terms **abuse, dependence and withdrawal** showed also an association with depression, and in two

out of the 12 reports suicide attempt was reported. Two of the patients that reported signs of depression had psychiatric histories. Due to the already discussed limitations of the system, and the few reports available, it is not known if depression is a sign of withdrawal.

American Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System (TESS). The cumulative AAPCC database (published in 1998) contains 22.6 million human poison exposure cases. These reports have been published in the ***American Journal of Emergency Medicine*** annually between 1983 and 1998. The 1998 AAPCC publication contains 2,192,088 human poison exposure cases reported by 66 participating poison centers during 1997, an increase of 1.7% compared with 1996 poisoning reports. Of the 66 reporting centers, 62 submitted data for the entire year. Forty-nine of the 66 participating centers were certified by AAPCC in 1997.

Extrapolations from the number of reported poisonings to the number of actual poisonings occurring annually in the US and trending of the data cannot be made from these data alone, because of considerable variations in poison center operations from year to year. Because of growth and development of the AAPCC data collection system, the increasing or changing center participation from year to year, the data do not directly identify a trend in overall incidence of poisonings in the U.S. Variations in reporting may be related to changes in funding that lead to diminished service. Such impaired service may lead to decreased surveillance efforts and a decrease in poison prevention activity. Changes may also reflect different degrees of public awareness of poison center services rather than an actual increase in poisonings. See **Table 10** below for annual changes in reporting centers, populations served, and reported human exposures. Approximately half of the fatalities result from suicide, and pediatric deaths usually comprise on an annual basis less than 5% of the total (**Table 11**).

TABLE 10. GROWTH OF THE AAPCC TOXIC EXPOSURE SURVEILLANCE SYSTEM

YEAR	Participating Centers (No.)	Population Served (Millions)	Human Exposures Reported	Exposures/Thousand Population
1983	16	43.1	251,012	5.8
1984	47	99.8	730,224	7.3
1985	56	113.6	900,513	7.9
1986	57	132.1	1,098,894	8.3
1987	63	137.5	1,166,940	8.5
1988	64	155.7	1,368,748	8.8
1989	70	182.4	1,581,540	8.7
1990	72	191.7	1,713,462	8.9
1991	73	200.7	1,837,939	9.2
1992	68	196.7	1,864,188	9.5
1993	64	181.3	1,751,476	9.7
1994	65	215.9	1,926,438	8.9
1995	67	218.5	2,023,089	9.3
1996	67	232.3	2,155,952	9.3
1997	66	250.1	2,192,088	8.8
TOTAL			22,562,503	

TABLE 11. 15-YEAR COMPARISONS OF FATALITY DATA

YEAR	Total Fatalities		Suicides		Pediatric Deaths	
	No.	% of cases	No.	% of cases	No.	% of deaths
1983	95	0.038	60	63.2	10	10.5
1984	293	0.040	165	56.3	21	7.2
1985	328	0.036	178	54.3	20	6.1
1986	406	0.037	223	54.9	15	3.7
1987	397	0.034	226	56.9	22	5.5
1988	545	0.040	297	54.5	28	5.1
1989	590	0.037	323	54.7	24	4.1
1990	612	0.036	350	57.2	25	4.1
1991	764	0.042	408	53.4	44	5.8
1992	705	0.038	395	56.0	29	4.1
1993	626	0.036	338	54.0	27	4.3
1994	766	0.040	410	53.5	26	3.4
1995	724	0.036	405	55.9	20	2.8
1996	726	0.034	358	49.3	29	4.0
1997	786	0.036	418	53.2	25	3.2

AAPCC Definitions. In order to use the AAPCC database that the sponsor submitted to make an assessment of reports of abuse of cyclobenzaprine, the following data were compiled: 1. Exposure duration (that is, acute versus chronic use); 2. Reason for use (that is, for abuse, misuse or suicide) by age with specific attention to that of minors (age groups less than 6 years, range of 6 to 12 years of age, range of 13-19 years, and 20 years or greater); 3. Medical outcome with specific attention to those toxic exposures that were described as moderate effect, major effect and death; and 4. Descriptions of the clinical reasons for the poison control center reports, followed by details of the cases of abuse, likely abuse or specific cases involving minors. (See **APPENDIX**).

Exposure Duration

The applicable terms are defined as follows: **Acute:** A single, repeated or continuous exposure occurring over a period of 8 hours or less. **Acute-on-chronic:** A single exposure that was preceded by a continuous, repeated or intermittent exposure occurring over a period exceeding 8 hours. **Chronic:** A continuous, repeated, or intermittent exposure to the same substance lasting longer than 8 hours. **Unknown:** Acute or chronic exposure cannot be determined.

More than 90% of cyclobenzaprine reports are attributed to acute exposures and 6.3% to acute-on-chronic exposures. One might expect in abuse situations to see repeated use of a substance. Overall, one percent of the cases were attributed to acute use with the intent to abuse the drug. One-tenth percent of the intent to abuse cases are defined as acute-on-chronic and chronic use (**Table 12**). The numbers are small, but there is little indication of repeated or long term use from this data.

TABLE 12. SUMMARY Cyclobenzaprine, Without Concomitants, Reason by Exposure Chronicity (1993-1997).

Reason	Acute	Acute-on-Chronic	Chronic	Unknown	Total (%)
Unintent.-Misuse	138 (1.6)	14 (0.2)	4 (<0.1)	2	158 (1.8)
Unintent.-Total	4469	181	39	13	4702
Intent-Susp Suicide	3014 (34.2)	289 (3.3)	9 (0.1)	144	3456 (39.2)
Intent.-Misuse	269 (3.0)	54 (0.6)	15 (0.2)	7	345 (3.9)
Intent.- Abuse	86 (1.0)	5 (<0.1)	5 (<0.1)	3	99 (1.1)
Intent.-Total	3516	374	32	183	4105
Contam/Tamper	3 (100)	0	0	0	3 (0.03)
Malicious	4 (80)	1 (20)	0	0	5 (0.05)
Total	7992 (90.7)	556 (6.3)	71 (0.8)	196 (2.2)	8815 (100)

Reason

The terms are defined as follows: **Unintentional Or Accidental general:** All unintentional exposures not specifically defined below. **Therapeutic error**: An unintentional deviation from a proper therapeutic regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance. Only exposures to medications or products substituted for medications are included. Drug interactions resulting from unintentional administration of drugs or foods which are known to interact are also included. **Unintentional misuse:** unintentional improper or incorrect use of a nonpharmaceutical substance. Unintentional misuse differs from intentional misuse in that the exposure was unplanned or not foreseen by patient. **Unintentional unknown:** Unintentional exposure, but reason not known. **Suspected suicidal:** Inappropriate use, suspected to be self-destructive or manipulative. **Intentional misuse**: Intentional improper or incorrect use of a substance for reasons other than pursuit of a psychotropic effect. **Intentional abuse:** Intentional improper or incorrect use of a substance where victim was likely attempting to achieve a euphoric or psychotropic effect. All recreational use of substances for any effect is included. **Intentional unknown:** Intentional, specific motive is unknown.
Contaminant/tampering: Patient is an unintentional victim of a substance that has been adulterated (either maliciously or unintentionally) by introduction of an undesirable substance. **Malicious:** Used to capture patients who are victims of another person's intent to harm them. **Adverse reaction:** Occurring with normal, prescribed, labeled or recommended use of product, as opposed to overdose, misuse, or abuse. Included are cases with an unwanted effect due to an allergic, hypersensitive or idiosyncratic response to the active ingredients, inactive ingredients, or excipients. Concomitant use of a contraindicated medication or food is excluded and coded instead as a therapeutic error.

See **Tables 13** and **14** below for reasons which lead to poison control reports for cyclobenzaprine without concomitant drugs and with all other agents, respectively. Each **Table** summarizes the reasons for the time period 1993-1997 and 1986-1992, respectively.

The time periods are presented in two time blocks (for this element and subsequent elements) and in separate tables, for the time period of 1993 to 1997 and periods of time

up to and including 1992. The reasons are as follows. Prior to 1993, the term "accidental" as opposed to "unintentional" use were used. Their meanings are essentially interchangeable, however. In addition, there was a small difference in the age categories in the two time periods. Prior to 1993, the teen years encompassed 13 to 17 years of age and the adult block was greater than 17 years of age. This was changed in 1993 to include 13 to 19 years of age for teens and 20 years or greater for adults. Also, from 1993, individual listings of clinical effects were provided for individual case reports. Relevant data are compiled in the **APPENDIX**. In addition, prior to 1993 the reasons for exposure did not include the categories of "contamination/tampering" and "malicious" exposure.

Approximately 6% involve teenage suspected suicide attempts. For the categories "Intent to Abuse" and "Intent to Misuse" by minors, there were 182 total reports which represents less than 1.0% of all reports. In addition, there were 5 reports of malicious use of the drug, of which three involved individuals who were 19 years of age or younger. Details of reports involving contamination, tampering and malicious use of the drug were not provided, except in one case that involved the sedation and murder of a victim.

TABLE 13. SUMMARY Cyclobenzaprine, Without Concomitants, Reason by Age (1993-1997).

Reason	<6 yrs	6-12 yrs	13-19 yrs	>= 20 yrs	Unknown	Total
Unintent-Misuse	10	35	16	94	3	158 (1.7%)
Intent-Susp Suicide	3	23	596	2765	69	3456 (38.2%)
Intent-Misuse	1	10	59	267	8	345 (3.8%)
Intent-Abuse	1	7	36	53	2	99 (1.1%)
Comtamin/tamper	1	1	0	1	0	3
Malicious	0	0	3	2	0	5
TOTAL	2658 29.4%	686 7.6%	936 10.3%	4644 51.3%	122	9046 (100%)

TABLE 14. SUMMARY: Cyclobenzaprine, Without Concomitants, Reason by Age (1986-1992).

Reason	<6 yrs	6-12 yrs	13-17 yrs	>17 yrs	Unknown	Total
Unintent-Misuse	31	94	30	298	14	467 (5.9%)
Intent-Susp Suicide	12	23	427	2516	95	3073 (38.7%)
Intent-Misuse	4	7	27	235	6	281 (3.5%)
Intent-Abuse	1	4	25	74	3	107 (1.3%)
Comtamin/tamper	-	-	-	-	-	-
Malicious	-	-	-	-	-	-
TOTAL	2716 34.2%	318 4%	642 8.1%	4054 51.1%	203 2.6%	7933 (100%)

As can be seen from the data in **Tables 15** and **16** which contain compiled data for cyclobenzaprine and all other agents during the two time periods, the suspected suicide attempts increased to 52.7% (16,660 suicide attempts out of a total of 31,584 poison control reports. The combined "Intent to Abuse" and "Intent to Misuse" cyclobenzaprine

with other substances was also increased to 1,808 out of 31,584 (5.7%). For minors, there were 2,569 Suicide Attempt reports (8.1%) and 307 "Intent to Abuse" and "Intent to Misuse" reports (1.0%).

TABLE 15. SUMMARY: Cyclobenzaprine, All Exposures, Reason by Age (1993-1997).

Reason	<6 yrs	6-12 yrs	13-19 yrs	>= 20 yrs	Unknown	Total
Unintent-Misuse	20	43	27	194	3	287 (1.6%)
Intent-Susp Suicide	5	49	1489	7684	127	9354 (53.6%)
Intent-Misuse	1	12	92	538	13	656 (3.8%)
Intent-Abuse	4	13	64	214	5	300 (1.7%)
Comtamin/tamper	1	1	0	2	0	4 (0.02%)
Malicious	0	0	5	6	0	11 (0.06%)
TOTAL	3197 (18.3%)	793 (4.5%)	2035 (11.7%)	11216 (64.3%)	209 (1.2%)	17451 (100%)

TABLE 16. SUMMARY: Cyclobenzaprine, All Exposures, Reason by Age (1986-1992).

Reason	<6 yrs	6-12 yrs	13-17 yrs	> 17 yrs	Unknown/ miss/inv	Total
Accident-Misuse	34	100	40	469	8	651 (4.6%)
Intent-Susp Suicide	22	42	942	6179	101	7306 (51.7%)
Intent-Misuse	4	10	50	486	9	559 (3.9%)
Intent-Abuse	1	6	50	233	3	293 (2.1%)
Comtamin/tamper	-	-	-	-	-	-
Malicious	-	-	-	-	-	-
TOTAL	3068 (21.7%)	376 (2.7%)	1286 (9.1%)	10085 (71.4%)	218 (1.5%)	14133 (100)

Medical Outcome

The applicable terms are defined as follows: **No effect**: Patient developed no signs or symptoms as a result of the exposure. **Minor effect**: Patient developed some signs or symptoms as a result of the exposure but they were minimally bothersome, and generally resolved rapidly with no residual disability of disfigurement. **Moderate effect:** Patient exhibited signs or symptoms as a result of the exposure which were more pronounced, more prolonged, or more of a systemic nature than minor symptoms. Usually some form of treatment is indicated. Symptoms were not life-threatening and patient has no residual disability or disfigurement. **Major effect**: Patient exhibited signs or symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement. **Death:** The patient died as a result of the exposure or as a direct complication of the exposure. Only those deaths which are probably or undoubtedly related to the exposure are coded here. **Not followed, judged as nontoxic exposure:** Substance implicated was nontoxic, amount insignificant, or route of exposure was unlikely to result in a clinical effect. **Not followed, minimal clinical effects possible:** Exposure was likely to result in only minimal toxicity of a trivial nature. **Unable to follow, judged as a potentially toxic exposure**: Lost to follow-up or refused follow-up, but exposure was significant and may have resulted in a moderate, major or fatal outcome. **Unrelated effect:** Exposure was probably not responsible for

the effect. **Confirmed nonexposure:** Exposure initially thought to have occurred actually never occurred.

Medical outcomes for the poison control reports are summarized in **Tables 17** and **18** for cyclobenzaprine without concomitant drugs, for the years 1993-1997 and 1985-1992, respectively. For the poison control reports for medical outcomes with other substances, summaries are compiled in **Tables 19** and **20**, respectively. Only two deaths for cyclobenzaprine alone were reported. However, there were 36 death reports for cyclobenzaprine with other agents. Combined categories of cyclobenzaprine without concomitants for "Moderate Effects", "Major Effects" and "Death" totaled 1,517 reports of 11,127 reports (13.6%). For minors, there were 375 of 11,127 reports (3.4%). Cyclobenzaprine with all other agents (**Tables 19** and **20**) resulted in 4,592 reports of 21,774 total reports (21.1%) for the categories "Moderate Effects", "Major Effects" and "Death." For minors, there were 795 of 21,774 such reports (3.7%).

TABLE 17. SUMMARY: Cyclobenzaprine, without concomitants, Medical Outcome by Age (1993-1997).

Report	<6 yrs	6-12 yrs	13-19 yrs	>= 20 yrs	Total
No effect	1553	213	181	643	2605 (44.7%)
Minor Effect	417	173	311	1370	2282 (39.2%)
Moderate effect	55	28	132	629	849 (14.6%)
Major effect	2	1	12	70	87 (1.5%)
Death	0	0	0	0	0
TOTAL	2027 (34.8%)	415 (7.1%)	636 (10.9%)	2712 (46.6%)	5823 (100)

TABLE 18. SUMMARY: Cyclobenzaprine, without concomitants, Medical Outcome by Age (1985-1992).

Report	<6	6-12	13-17	>17	Total
No effect	1636	87	118	545	2402 (45.3%)
Minor Effect	466	79	262	1488	2321 (43.8%)
Moderate effect	45	10	64	372	494 (9.3%)
Major effect	2	1	14	69	85 (1.6%)
Death	0	0	0	2	2 (0.04%)
TOTAL	2149 (40.5%)	177 (3.3%)	458 (8.6%)	2476 (46.7%)	5304 (100%)

TABLE 19. SUMMARY: Cyclobenzaprine, All Exposure, Medical Outcome by Age (1993-1997).

Report	<6 yrs	6-12 yrs	13-19 yrs	>= 20 yrs	Total
No effect	1817	243	380	1436	3900 (32.7%)
Minor Effect	489	201	727	3674	5110 (42.8%)
Moderate effect	70	42	357	1975	2455 (20.6%)
Major effect	2	1	34	411	453 (3.8%)
Death	0	0	1	18	19 (0.16%)
TOTAL	2378 (19.9%)	487 (4.1%)	1499 (12.6%)	7514 (62.9%)	11937 (100%)

TABLE 20. SUMMARY: Cyclobenzaprine, All Exposure, Medical Outcome by Age (1985-1992).

Report	<6 yrs	6-12 yrs	13-17 yrs	>17 yrs	Total
No effect	1855	101	227	1101	3307 (33.6%)
Minor Effect	531	96	590	3606	4865 (49.5%)
Moderate effect	58	15	153	1135	1369 (13.9%)
Major effect	4	2	28	243	279 (2.8%)
Death	0	0	2	15	17 (0.17%)
TOTAL	2448 (24.9%)	214 (2.2%)	1000 (10.2%)	6100 (62.0%)	9837 (100%)

Drug related clinical effects (cumulative for 1995 to 1997) are listed in **Table 21** below. Neurologic and cardiovascular effects accounted for 85% of the total. In cases wherein cyclobenzaprine was the only drug involved, the primary clinical effects reported to poison control centers, were drowsiness/lethargy (43.9%), tachycardia (13%), agitation/irritability (6.4%), slurred speech (3.6%), confusion (3.1%), coma (2.9%), dizziness/vertigo (2.9%), vomiting (2.3%), ataxia (1.8%), hallucinations (1.6%), hypertension (1.6%), and respiratory depression (1.4%). The following section (see **APPENDIX**) describes in greater detail selected cases of abuse or suspected suicide in which abuse was considered possible and includes the medical outcome and clinical effects resulting from concomitant use of cyclobenzaprine with other agents, including alcohol, benzodiazepines, cocaine and other substances.

TABLE 21. CYCLOBENZAPRINE – WITHOUT COMCOMITANTS AAPCC – DISTRIBUTION OF DRUG RELATED CLINICAL EFFECTS.

EFFECTS	1997	1996	1995	1995-1997
CARDIOVASCULAR	**221**	**204**	**209**	**634 (16.4%)**
Bradycardia	2 (0.2%)	2 (0.2%)	4 (0.3%)	
Cardiac Arrest	0	0	1 (0.1%)	
Conduction disturbance	10 (0.8%)	5 (0.4%)	5 (0.4%)	
Dysrhythmia (other)	1 (0.1%)	4 (0.3%)	2 (0.2%)	
Dysrhythmia (VT/VF)	0	0	1 (0.1%)	
Hypotension	15 (1.1%)	4 (0.3%)	16 (1.3%)	35 (0.9%)
Hypertension	22 (1.7%)	24 (1.9%)	16 (1.3%)	62 (1.6%)
Tachycardia	171 (12.9%)	165 (13.0%)	164 (12.9%)	500 (13.0%)
DERMAL	**18**	**14**	**9**	**41 (1.1%)**
Edema	2 (0.2%)	0	0	
Erythema/flushed	9 (0.7%)	7 (0.55%)	3 (0.2%)	
Irritation/pain	1 (0.1%)	1 (0.1%)	0	
Pallor	1 (0.1%)	2 (0.2%)	2 (0.2%)	
Pruritus	1 (0.1%)	3 (0.2%)	2 (0.2%)	
Puncture wound/sting	1 (0.1%)	1 (0.1%)	0	
Rash	3 (0.2%))	0	2 (0.2%)	
GASTROINTESTINAL	**41**	**56**	**62**	**159 (4.1%)**
Abdominal Pain	6 (0.5%)	4 (0.3%)	5 (0.4%)	
Anorexia	1 (0.1%)	0	0	
Constipation	0	1 (0.1%)	1 (0.1%)	
Diarrhea	1 (0.1%)	2 (0.2%)	0	
Nausea	5 (0.4%)	17 (1.4%)	22 (1.7%)	44 (1.1%)
Oral Irritation	1 (0.1%)	1 (0.1%)	2 (0.2%)	
Throat Irritation	1 (0.1%)	2 (0.2%)	0	
Vomiting	26 (2.0%)	29 (2.3%)	32 (2.5%)	87 (2.3%)
HEMATOLOGIC/ HEPATIC	**0**	**0**	**0**	**0**
AST, ALT>100<=1,000	0	0	0	
AST, ALT > 1,000	0	0	0	
Bilirubin elevated	0	0	0	
PT Prolonged	0	0	0	
Other coagulopathy	0	0	0	
Other LFT abnormality	0	0	0	
NEUROLOGIC	**908**	**859**	**854**	**2621 (68.0%)**
Agitated/Irritable	91 (6.9%)	82 (6.5%)	75 (5.9%)	248 (6.4%)
Ataxia	26 (2.0%)	25 (2.0%)	19 (1.5%)	70 (1.8%)
Coma	34 (2.6%)	39 (3.1%)	40 (3.1%)	113 (2.9%)
Confusion	41 (3.1%)	41 (3.2%)	36 (2.8%)	118 (3.1%)
Dizziness/Vertigo	37 (2.8%)	36 (2.9%)	37 (2.9%)	110 (2.9%)
Drowsiness/Lethargy	591 (44.6%)	547 (43.3%)	554 (43.7%)	1692 (43.9%)
Dystonia	1 (0.1%)	2 (0.16%)	2 (0.2%)	
Hallucination/delusion	18 (1.4%)	17 (1.4%)	27 (2.1%)	62 (1.6%)
Headache	4 (0.3%)	3 (0.24%)	2 (0.2%)	
Muscle Rigidity	2 (0.2%)	2 (0.2%)	1 (0.1%)	
Muscle Weakness	3 (0.2%)	5 (0.4%)	6 (0.5%)	
Peripheral neuropathy	1 (0.1%)	1 (0.1%)	2 (0.2%)	

Seizure (single)	3 (0.2%)	2 (0.2%)	3 (0.2%)	
Seizures (>1 discrete)	0	2 (0.2%)	1 (0.1%)	
Slurred Speech	49 (3.7%)	45 (3.6%)	43 (3.4%)	137 (3.6%)
Syncope	0	1 (0.1%)	1 (0.1%)	
Tremor	7 (0.5%)	9 (0.7%)	5 (0.4%)	
OCULAR	**22**	**22**	**18**	**62 (1.6%)**
Blurred vision	5 (04%)	4 (0.3%)	2 (0.2%)	
Irritation/pain	3 (0.2%)	1 (0.1%)	2 (0.2%)	
Miosis	2 (0.2%)	3 (0.2%)	4 (0.3%)	
Mydriasis	11 (0.8%)	14 (1.1%)	9 (0.7%)	34 (0.9%)
Nystagmus	1 (0.1%)	0	1 (0.1%)	
RENAL/GU	**2**	**6**	**11**	**19 (0.5%)**
Creatinine elevated	0	0	1 (0.1%)	
Oliguria/anuria	0	2 (0.2%)	2 (0.2%)	
Renal failure	0	0	1 (0.1%)	
Urinary incontinence	2 (0.2%)	1 (0.1%)	2 (0.2%)	
Urinary retention	0	3 (0.2%)	5 (0.4%)	
RESPIRATORY	**24**	**29**	**25**	**78 (2.0%)**
Bronchospasm	0	1 (0.1%)	0	
Cough/choke	0	2 (0.2%)	2 (0.2%)	
Dyspnea	3 (0.2%)	3 (0.3%)	2 (0.2%)	
Hyperventilation/tachy	1 (0.1%)	2 0.2%)	1 (0.1%)	
Pneumonitis	1 (0.1%)	1 (0.1%)	1 (0.1%)	
Pulmonary edema	0	0	0	
Respiratory arrest	1 (0.1%)	1 (0.1%)	1 (0.1%)	
Respiratory depression	18 (1.4%)	19 (1.5%)	18 (1.4%)	55 (1.4%)
MISCELLANEOUS	**86**	**66**	**73**	**225 (5.8%)**
Acidosis	5 (0.4%)	5 (0.4%)	3 (0.2%)	
ADR to treatment	11 (0.8%)	6 (0.5%)	3 (0.2%)	
Anion gap	0	1 (0.1%)	0	
Diaphoresis	0	0	2 (0.2%)	
Electrolyte abnormality	1 (0.1%)	3 (0.2%)	3 (0.2%)	
Fever/hyperthermia	3 (0.2%)	7 (0.6%)	3 (0.2%)	
Hyperglycemia	0	0	1 (0.1%)	
Hypoglycemia	0	0	1 (0.1%)	
Hypothermia	0	1 (0.1%)	2 (0.2%)	
OTHER	66 (5.0%)	43 (3.4%)	55 (4.3%)	164 (4.3%)
TOTAL	**1325 (100)**	**1263 (100)**	**1267 (100)**	**3855 (100)**

Summary and Conclusions.

1.The abuse potential of cyclobenzaprine has not been studied by the standard preclinical assessment studies (drug discrimination, self-administration and dependence studies) that are usually recommended and used in the evaluation of new drugs.

2. DAWN/ED: Frequency of ED mentions relative to the total number of prescriptions for 1992-1997 for cyclobenzaprine is approximately 4 mentions per ten thousand prescriptions. By comparison, the frequency of ED mentions per ten thousand prescriptions is approximately 10 for carisoprodol and 11 for diazepam.

3. DAWN/ED: 7.6 percent of the cyclobenzaprine ED mentions were in the age group 6-17 years. 58.1% were females. Reason for the ED visit was primarily overdose (88.2%) with the motive of committing suicide (74%). Other lesser motives for cyclobenzaprine use that were reported were dependence (3.5%), recreational use (1.4%), and for other psychic effects (10.8%).

4. DAWN/ED: Concomitant substance used with cyclobenzaprine was alcohol (36.1%). Other substances taken in combination with cyclobenzaprine were drugs of abuse (amphetamine, heroin, oxycodone, hydrocodone, hydromorphone, methamphetamine, and marijuana), all at <0.1%.

5. DAWN/ME: Frequency of reported medical examiner mentions relative to prescriptions for cyclobenzaprine and the comparators showed that reporting rat for diazepam is approximately 19 times greater and approximately 4 times greater for carisoprodol than for cyclobenzaprine.

6. DAWN/ME: Drugs associated with the deaths for cyclobenzaprine were alcohol (33), heroin/morphine (31), cocaine (25), and other opiates (codeine, oxycodone, hydrocodone, and methadone).

7. AERS: Twelve cyclobenzaprine reports were associated with the terms, abuse, dependence and withdrawal. These reports were also associated with depression and 2 of the 12 reports also concerned suicide attempts. Due to the limitations of such reports as described above, and the few reports available, it is not known if depression was a sign of withdrawal.

8. AAPCC: More than 90% of cyclobenzaprine reports are attributed to acute exposures and 6.3% to acute-on-chronic exposures.

9. AAPCC: Suicide attempt was by far the largest reason that resulted in a toxic exposure to cyclobenzaprine. There was an increasing percentage of suicide attempts and successes, as well as intent to abuse and misuse when cyclobenzaprine was used in combination with other substances.

10. AAPCC: Approximately 6 to 8 percent of the suicide attempt reports involved minors (primarily teenagers).

11. AAPCC: Most details of reports that described the detailed circumstances of contamination, tampering and malicious use of the drug were not provided.

12. AAPCC: Combined categories of cyclobenzaprine without concomitants for "Moderate Effects," "Major Effects," and "Death" comprised 13.6% of toxic exposures; 3.4% of all such reports involved minors.

13. AAPCC: Combined categories of cyclobenzaprine with all other agents for "Moderate Effects," "Major Effects," and "Death" comprised 21.1% of toxic exposures; 3.7% of all such reports involved minors.

14. AAPCC: Cyclobenzaprine deaths were reported for cyclobenzaprine alone, but primarily in combination with other drugs: alcohol, benzodiazepines, opiates (codeine, oxycodone, propoxyphene), phenothiazine, aspirin, acetaminophen, ibuprofen, oral hypoglycemics, cocaine, amitriptyline, desipramine, doxepin, imipramine, diphenhydramine, calcium antagonists, antirhythmics (quinidine, bretylium, procainamide, etc.). (See**APPENDIX**).

10. AAPCC: Cyclobenzaprine "major effect" or "potentially toxic effect" for medical outcome resulted from cyclobenzaprine in combination with alcohol, other sedative-hypnotics (antianxiety or antipsychotic agents), benzodiazepines, barbiturate, opiates (including propoxyphene, codeine, oxycodone pentazocine), amitriptyline, nortriptyline, imipramine (antidepressants of the phenothiazine type), other skeletal muscle relaxants, meprobamate, drugs of abuse (including cocaine, amphetamine and related compounds, phencyclidine, hallucinogenic mushrooms), antihistamines, diphenhydramine, furosemide, and anticholinergic substances.

11. In cases wherein cyclobenzaprine was the only drug involved, the primary clinical effects reported to poison control centers, were drowsiness/lethargy (43.9%), tachycardia (13%), agitation/irritability (6.4%), slurred speech (3.6%), confusion (3.1%), coma (2.9%), dizziness/vertigo (2.9%), vomiting (2.3%), ataxia (1.8%), hallucinations (1.6%), hypertension (1.6%), and respiratory depression (1.4%).

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APPENDIX

FLEXERIL - AAPCC DATA - MEDICAL OUTCOME: ABUSE WITH OTHER SUBSTANCES

1985 Medical outcome

Moderate Effect: None

Unknown nontoxic effect: None

Unknown potentially toxic effect: None

1986 Medical outcome

Moderate Effect: None

Unknown nontoxic effect: None

Unknown potentially toxic effect: None

1987 Medical outcome:

Moderate Effect:
Abuse 6-24-87 26 y F w/PCP
Abuse 7-17-87 22 y M w/aminophylline/theophylline

Unknown potentially toxic effect
Abuse 11-21-87 24 y M w/ethanol (beverage)
Abuse 8-28-87 unk y M w/unknown type of alcohol
Abuse 6-23-87 32 y M w/benzodiazepines
Abuse 6-13-87 31 y M w/caffeine
Abuse 8-24-87 26 y M w/heroin parenteral
Abuse 2-16-87 unk y F w/ethanol (beverage)
Abuse 10-1-87 unk y U w/APAP w/propoxyphene
Abuse 7-3-87 unk y M w/ethanol (non-beverage, non-rubbing)

Deaths:
Suicidal 3-10-87 19 y M w/Propoxyphene

1988 Medical outcome:

Moderate Effect
Abuse 4-1-88 20 y M w/benzodiazepines (inhalation)
Abuse 1-19-88 26 y M w/benzodiazepines
Abuse 8-1-88 27 y M w/benzodiazepines

Unknown nontoxic effect:
Abuse 11-27-88 21 y M w/marijuana

Unknown potentially toxic effect
Abuse 3-4-88 unk y F w/amphetamines & related compounds

Abuse 7-17-88 19 y M w/ethanol (beverage)
Abuse 12-1-88 unk y M w/ethanol (beverage)
Abuse 2-23-88 unk y M w/misc unk drugs
Abuse 4-17-88 28 y M w/cocaine
Abuse 7-20-88 19 y M w/ASA codeine
Abuse 12-27-88 32 y M w/ethanol (beverage)
Abuse 11-16-88 26 y M w/APAP w/propoxyphene

Major Effect:

Suicidal 8-1-88 14 y F w/ Propoxyphene
Suicidal 7-31-88 17 y F Only Cyclobenzaprine
Suicidal 9-22-88 38 y M w/Ethanol (beverage)
Suicidal 1-13-88 14 y F w/ Propoxyphene
Acc General 1-22-88 39 y F w/Ethanol (beverage)
Suicidal 7-18-88 28 y M w/Ethanol (beverage)

Death:

Suicidal 10-23-88 24 y F w/ Antidepressant and Phenothiazine
Suicidal 8-24-88 49 y F w/ Aspirin
Intent. Unknown 10-16-88 22 y M w/APAP & Codeine

1989 Medical outcome:

Moderate Effect
None

Unknown nontoxic effect:
Abuse 6-17-89 unk y M w/ethanol (beverage)

Unknown potentially toxic effect
Abuse 2-18-89 33 y M w/benzodiazepines
Abuse 3-15-89 unk y F w/cocaine (inhalation)
Abuse 11-11-89 45 y M w/unknown type of alcohol
Abuse 11-9-89 19 y F w/marijuana (inhalation)
Abuse 9-23-89 unk y M w/APAP w/propoxyphene
Abuse 8-3-89 16 y M w/APAP w/codeine
Abuse 8-30-89 unk y F w/ethanol (beverage)
Abuse 12-5-89 27 y M w/ethanol (beverage)
Abuse 6-4-89 18 y F w/misc unk drugs

Major Effects:

Suicidal 12-17-89 UA y F w/ Pentazocine
Suicidal 2-25-89 34 y F w/Ethanol
Suicidal 11-4-89 25 y M w/Ethanol
Suicidal 2-19-89 49 y M w/Benzodiazepines
Unknown Reasons 11-17-89 17 y F Re: food products, additives, or supplements
ADR Drug 12-14-89 UA y M w/Meprobamate
Suicidal 4-11-89 17 y F Only Cyclobenzaprine
ADR Drug 6-14-89 27 y F w?Benzodiazepines
Suicidal 8-6-89 30 y F w/Meprobamate
Suicidal 8-8-89 27 y F w/Diphenhydramine (Unk if OTC or Rx)

Deaths:

Suicidal 3-29-89 19 y M Only Cyclobenzaprine
Suicidal 10-1-89 46 y F w/APAP with Propoxyphene

Suicidal 8-25-89 33 y F w/Desipramine

1990 Medical outcome:

Moderate Effect:

Abuse 8-18-90 61 y F w/ethanol (beverage)
Abuse 6-10-90 unk y M w/ethanol (beverage)
Abuse 12-9-90 16 y M w/ethanol (beverage)

Unknown nontoxic effect:

Abuse 2-12-90 29 y F w/ASA plus other formulation
Abuse 2-15-90 29 y F w/ASA plus other formulation
Abuse 3-23-90 37 y M w/pentazocine
Abuse 3-29-90 31 y M w/unknown type of alcohol

Unknown potentially toxic effect:

Abuse 3-5-90 34 y M w/ethanol (beverage)
Abuse 7-14-90 unk y F w/cocaine
Abuse 2-15-90 34 y M w/ethanol (beverage)
Abuse 6-15-90 65 y M w/ethanol (beverage)
Abuse 10-4-90 unk y M w/amitriptyline
Abuse 12-2-90 unk y F w/benzodiazepines
Abuse 9-10-90 unk y M w/ethanol (beverage)
Abuse 7-19-90 unk y F w/ethanol (beverage)
Abuse 7-28-90 23 y F w/ethanol (beverage)
Abuse 8-29-90 unk y M w/ethanol (beverage)
Abuse 6-5-90 25 y M w/cocaine

Major Effect:

Suicidal 10-23-90 15 y F w/Diphenhydramine (OTC)
Suicidal 10-20-90 34 y M w/Ethanol (beverage)
Suicidal 4-5-90 42 y M W/Ethanol (beverage)
Suicidal 12-15-90 13 y F w/Benzodiazepines
Suicidal 12-23-90 15 y F Only cyclobenzaprine
Suicidal 5-27-90 21 y F w/Ethanol (beverage)
Suicidal 8-19-90 21 y F w/Ethanol (Beverage)
Unknown Reason 8-17-90 35 y M w/Ethanol (Beverage)
Suicidal 12-19-90 17 y F w/Thiazide
Int Misuse 7-22-90 UA y M Only cyclobenzaprine
Suicidal 2-24-90 17 y M with unknown formulation of APAP
Suicidal 3-5-90 16 y M Only cyclobenzaprine
Suicidal 4-1-90 16 y F w/APAP with codeine
Suicidal 7-10-90 16 y F w/Nortriptyline
Suicidal 9-9-90 13 y F Only Cyclobenzaprine
Int Misuse 1-17-90 37 y F Only Cyclobenzaprine

Death:

Suicidal 9-7-90 15 y F w/Oral hypoglycemics
Suicidal 6-11-90 45 y M Only Cyclobenzaprine
Abuse 6-10-90 30 y M w/Cocaine (Inhalation, parenteral)

1991 Medical outcome:

Moderate Effect:

Abuse 7-2-91 29 y M w/APAP w/oxycodone

Unknown nontoxic effect:
Abuse 5-2-91 13 y F w/antihistamine without PPA

Unknown potentially toxic effect:
Abuse 7-13-91 unk y M w/benzodiazepines
Abuse 8-22-91 37 y F w/benzodiazepines
Abuse 2-10-91 40 y M w/antihistamines
Abuse 5-18-91 15 y F w/other sed-hyp,antianxiety, or psychtropic drug
Abuse 12-20-91 40 y M w/oxycodone
Abuse 3-19-91 unk y F w/benzodiazepines
Abuse 8-9-91 34 y F w/ethanol (beverage)
Abuse 7-13-91 26 y F w/APAP w/other narcotic
Abuse 3-10-91 unk y M w/ethanol (beverage)
Abuse 10-20-91 37 y M w/ethanol (beverage)
Abuse 1-10-91 unk y M w/ethanol (non-beverage, non-rubbing)
Abuse 4-26-91 12 y M w/ethanol (beverage)
Abuse 1-6-91 25 y M w/ethanol (beverage)
Abuse 4-26-91 24 y M w/APAP w/other narcotic
Abuse 11-1-91 16 y F w/marijuana

Major Effect:
Int Unknown 9-25-91 23 y F w/Antihistamines (excluding cough/cold preparations)
Suicidal 8-18-91 UA y F w/Ethanol (beverage)
Int Unknown 3-15-91 33 y M w/Cocaine
Suicidal 10-6-91 28y F w/Ethanol (beverage)
Suicidal 3-7-91 36 y F w/Ethanol (beverage)
Suicidal 6-11-91 39 y F w/Ethanol (beverage)
Int Unknown 7-11-91 23 y M w/other Skeletal Muscle Relaxant

Death:
Suicidal 12-20-91 20 y M w/Ibuprofen (not known if Rx or OTC)

1992 Medical Outcome:

Moderate Effect
Abuse 11-30-92 18 y M LSD & cyclobenzaprine
Abuse 12-4-92 20 y M w/ ethanol (inhalation)
Abuse 11/21/92 43 y F w/ethanol (beverage)
Abuse 8-30-92 33 y M w/ethanol (beverage)

Unknown nontoxic effect:
Abuse 9-14-92 parenteral cyclobenzaprine F unk age

Unknown potentially toxic effect
Abuse 6-18-92 22 y M furosemide w/cyclobenzaprine
Abuse 7-2-92 6 mo. M
Abuse 2-6-92 18 y F w/benzodiazepines

Unrelated effect:
Abuse 3-29-92 43 y F w/benzodiazepines

Major Effect:
Suicidal 9-17-92 43 y M w/Ethanol (beverage)
Suicidal 9-17-92 41 y M w/Ethanol (beverage)
Abuse 7-17-92 28 y M w/PCP

Suicidal 2-7-92 24 y M w/Ethanol (beverage)
Suicidal 5-29-92 U y M w/Ethanol (beverage)
Suicidal 9-12-92 21 y M w/Ethanol (beverage)
Suicidal 5-9-92 30 y M w/Meprobamate
Suicidal 10-31-92 33 y M w/ Ethanol (beverage)
Suicidal 12–27-92 32 y Mw/Ethanol (beverage)
Suicidal 2-8-92 18 y M w/Benzodiazepines
Suicidal 6-13-92 38 y F w/Other Skeletal Muscle Relaxant
Suicidal 7-16-92 15 y M Only Cyclobenzaprine
Suicidal 5-31-92 16 y F Only Cyclobenzaprine
Suicidal 8-12-92 32 y M w/Ethanol (beverage)
Suicidal 10-20-92 46 y F w/Imipramine

Death:

Suicidal 11-1-92 26 y M w/Amitriptyline
Suicidal 4-19-92 58 y M w/Desipramine
Suicidal 1-18-92 26 y F w/Doxepin
Suicidal 10-23-92 32 y F w/Imipramine
Suicidal 10-18-92 25 y M w/Diphenhydramine
Suicidal 5-31-92 22 y F w/Calcium antagonists

1993 Medical Outcome:

Moderate Effect:

Abuse 8-24-93	53 y	F w/Phenothiazines S6,1
Susp suicide 3-24-93	***15 y***	***M w/marijuana*** **N7,1 N10,1**
Abuse 9-4-93	16 y	F w/ASA combo w/other comb formulation N7,1
Abuse 2-23-93	30 y	M w/ethanol (beverage)
Abuse 9-3-93	UA y	M w/other NSAID N6,1 N7,1 N20,1

NF/Judged nontoxic effect: None

NF/Minimal effect possible:

Abuse 3-30-93	18 y	F w/APAP in combo w/Propoxyphene M18,1
Abuse 10-28-93	UA y	F w/ethanol (beverage) N7,1
Abuse 9-24-93	34 y	M w/benzodiazepines N6,1

Unable to follow, potentially toxic:

Abuse 7-26-93 30 y F w/benzodiazepines N7,1
Abuse 2-11-93 41 y F w/APAP in combo w/Oxycodone
Abuse 5-4-93 25 y M w/ethanol (non-beverage, non-rubbing) N2,1 N4,1 N7,1 N20, 1
Abuse 10-13-93 20 y M w/APAP in combo w/Oxycodone
Abuse 11-16-93 18 y F w/benzodiazepines
Abuse 10-06-93 UA y F w/benzodiazepines

Major Effect:

Susp Suicide 12-8-93 18 y F w/ Other Skeletal muscle relaxant H1,1 N1,1 N3,1 O10,1 S9,1 M18,1
Susp Suicide 5-23-93 54 y F w/Amitriptyline C8,1 C9,1 N1,1 N3,1
Susp Suicide 11-8-93 19y F Only Cyclobenzaprine C8,1 C9,1 N4,1 N7,1 N10,1
Susp Suicide 12-16-93 18 y F w/Oral Hypoglycemics C9,1 G12,1 G16,1 N1,1
Susp Suicide 12-11-93 42 y M w/Ethanol (beverage) C7,1 N3,1
Susp Suicide 12-12-93 25 y M w/Ethanol (beverage) G12,1 N3,1 M18,1
Susp Suicide 3-9-93 U y U w/Ethanol (beverage) N3,1 N4,1 N7,1 S9,1
Susp Suicide 12-25-93 33 y M w/Ethanol (beverage) C8,3 C9,1 N3,1 S9,1
Acc General 7-13-93 27 y M w/Ethanol (Beverage) C8,1 C9,1 N7,1

Susp Suicide 3-18-93 32 y M w/Amphetamines C8,1 C9,1 N1,1 N7,1 S9,1
Int Unknown 2-10-93 20 y M w/Ethanol (beverage) N3,1 M12,1
Int Unknown 2-10-93 20 y M w/Ethanol (beverage) N3,1 M12,1
Susp Suicide 6-5-93 23 y M w/Ethanol (beverage) C9,1 G16,1 N1,1 N3,1 N7,1 O10,1
Susp Suicide 1-3-93 20s y M w/Methocarbromal C7,1 C9,1 N7,1 N17,1 M18,1
Susp Suicide 12-1-93 27 y F w/Cocaine N3,1
Susp Suicide 12-11-93 28 y M w/Ethanol (beverage) N7,3
Susp Suicide 5-6-93 30 y M w/Ethanol (beverage) C8,1 C9,1 N1,3 N7,1 N10,1 N23,1 S8,3
Susp Suicide 2-26-93 12 y F Only Cyclobenzaprine C9,1 N7,1 S9,1
Susp Suicide 5-11-93 31 y M w/other skeletal Muscle relaxant N3,1 N7,1 M18,1
Susp Suicide 1-8-93 33 y M w/Other skeletal Muscle relaxant S9,1
Susp Suicide 3-17-93 23 y F w/PCP N1,1 N7,1

Death:

Susp Suicide 3-3-93 42 y F w/Benzodiazepines C7,1 C9,1 N3,1 N17,1 M10,1
Susp Suicide 10-17-93 46 y F W/Codeine C2,1 N3,1 S8,1
Susp Suicide 1-10-93 22 y F w/APAP combin. C2,1 C9,1 R6,1 M7,1

1994 Medical Outcome:

Moderate effect:

Abuse 1-26-94 28 y M w/ethanol (beverage) C9,1 N1,1 N3,1
Malicious 7-18-94 14 y w/Phenothiazines N7,1 N8,1 R1,1 M18,1
Abuse 12-24-94 21 y M w/marijuana C8,1 C9,1 N1,1
Abuse 4-1-94 23 y F w/benzodiazepines N7,1
Abuse 3-21-94 46 y F w/ethanol (beverage) N7,1 N23,1 C8,1 C9,1
Abuse 3-8-94 24 y M w/ethanol (beverage) C9,1 N3,1 S9,1
Abuse 8-16-94 34 y M w/cough cold preparation (exclud DM, PPA)C9,1N10,1N11,1

Not followed, judged nontoxic: None

Not followed, minimal effects possible:

Abuse 7-26-94 33 y F w/ethanol (beverage) N6,1
Abuse 4-23-94 37 y F w/ethanol (beverage) N7,1

Unable to follow, potentially toxic:

Abuse 6-20-94 26 y M w/amphetamines & related compounds
Abuse 2/2/94 27 y F w/ APAP/Oxycodone
Abuse 7-8-94 20s y M w/ethanol (beverage)
Abuse 11-4-94 29 y M w/ethanol (beverage) N2,1 N 20,1
Abuse 5-7-94 UA y M w/ethanol (beverage)
Abuse 11-19-94 23 y M w/ethanol (beverage) N1,3 M7, 3 M 18,3
Abuse 6-11-94 20s y M w/cocaine (inhal/Nasal)
Abuse 12-31-94 UA y F w/ethanol (beverage)
Abuse 6-12-94 28 y M w/ethanol (beverage) N7,1
Abuse 3-5-94 U y M w/cocaine (unknown)
Abuse 2-1-04 U y F w/APAP & other narcotic N 20,1
Abuse 11-5-94 29 y M w/ethanol (beverage) N7,1 N2,1 N20,1

Major Effect:

Susp Suicide 8-10-94 16 y F w/APAP combin. N3,1 M18,1
Susp Suicide 4-9-94 15 y F w/APAP combin. C9,1 N1,1 N4,1 N7,1 N10,1
Susp Suicide 3-9-94 19 y M Only Cyclobenzaprine C7,1 N3,1 N7,1 M18,1
Susp Suicide 10-29-94 40 y F w/Ethanol (beverage) H1,1 H9,1 N7,1
Susp Suicide 5-29-94 43 y M w/Ethanol (beverage) N7,1

Susp Suicide 11-13-94 31 y F w/Other skeletal muscle relaxant C9,1 N3,1 N7,1
Susp Suicide 2-18-94 16 y F w/Other Antihistamines N1,1 N3,1 N7,1
Susp Suicide 11-7-97 18 y F Only Cyclobenzaprine N3,1 N4,1 R7,1 M1,1
Susp Suicide 10-22-94 33 y M w/Cocaine C8,1 C9,1 N1,1 N3,1 N7,1 M1,1 M3,1 M4,1 M7,3 M8,3 M11,3
Susp Suicide 3-13-94 34 y M w/Ethanol (beverage) N7,1 S9,1
Susp Suicide 5-23-94 15 y F Only Cyclobenzaprine N1,1 N3,1 N7,1 S9,1
Susp Suicide 11-5-94 24 y F w/Ethanol (beverage) C5,1 C9,1 G16,1 N3,1
Susp Suicide 6-7-94 30s y F w/Ethanol (beverage) N3,1 N7,1 S9,1
Susp Suicide 2-18-94 18 y M w/Nortriptyline C9,1 N7,1 M18,1
Susp Suicide 9-20-94 37 y F w/Diphenhydramine C8,1 C9,1 N3,1
Susp Suicide 11-27-94 31 y F w/Ethanol (beverage) N1,1 N3,1 N10,1 S9,1

Deaths:

Susp Suicide 10-28-94 41 y F w/Benzodiazepines C2,1 S8,1
Susp Suicide 4-12-94 15 y M w/Imipramine N7,1 C2,1 C6,1 G16,1 N17,1

1995 Medical Outcome:

Moderate effect:

Abuse 4-13-95 27 y M w/cocaine Iinhal.Nasal) C8,1 C9,1 M18,1
Abuse 1-25-95 60 y F No other med. N1,1 N4,1 N17,1 N20,1 M18,1
Abuse 5-17-95 17 y F No other med. N1,1 N3,1 N4,1 N7,1 N20,1
Abuse 8-30-95 12 y M No other med. N4,3 N7,1
Abuse 6-22-95 41 y M w/other skeletal muscle relaxant C9,1 N2,1 N4,1 N7,1 O8,1

Not followed, judged nontoxic: None

Not followed, minimal effects possible:

Abuse 1-2-95 UA y F w/Other NSAID
Abuse 7-7-95 48 y M w/Other NSAID N1,3 M18,3
Abuse 9-24-95 20 y F w/ethanol (beverage) D6,1 M18,1

Unable to follow, potentially toxic:

Abuse 5-21-95 35 y M w/Amphetamines & rel. cmpds (parenteral) M16,1 M18,1
Abuse 5-29-95 24 y M w/ethanol (beverage)
Abuse 11-11-95 24 y M w/benzodiazepines
Abuse 3-15-95 UA y F w/Anticholinergic (exclu cough/cold prep) N1,3
Abuse 4-22-95 35 y M w/Amitriptyline G12,1 G16,1
Abuse 11-5-95 16 y F w/antidepressant-phenothiazine N7,1
Abuse 4-27-95 39 y M w/Short&Intermed. Barbiturate G16,1 N7,1

Unrelated Effect:

Abuse 12-25-95 12 y F w/Calcium antagonists C4,3 N7,3
Abuse 12-17-95 26 y M w/ethanol (beverage) M18,3

Major Effect:

Susp Suicide 9-10-95 22 y F w/Ethanol (beverage) C8,1 C9,1 N1,1 N10,1
Susp Suicide 8-21-95 25 y F w/Ethanol (beverage) C9,3 N3,1 N7,1 S9,1 M13,1
Susp Suicide 4-19-95 15 y F w/Antibiotic prep (systemic) N10,1
Susp Suicide 4-11-95 15 y M w/ Antihistamines O7,1 S9,2
Susp Suicide 8-9-95 20 y F w/Amphetamines & Related Compds C8,3 C9,1 G16,1 N3,1
Susp Suicide 9-29-95 19 y F w/APAP & Oxycodone C9,1 D13,2 N3,1 N4,1
Unknown 9-18-95 17 y M w/Diphenhydramine G16,1 N1,1 N3,1 N7,1
Susp Suicide 1-13-95 50s y F Only Cyclobenzaprine C9,1 N3,1 N7,1 S9,1
Susp Suicide 3-15-95 50 y F w/Ethanol (beverage) N3,1 N7,1

Susp Suicide 6-16-95 30s y F w/Cocaine N3,1 N7,1 O7,1
Susp Suicide 6-16-95 14 y F Only Cyclobenzaprine C9,1 N3,1 N7,1 R8,1
Acc General 8-15-95 20 y M w/Ethanol (beverage) C9,1 N1,1 N3,1 S9,1
Abuse 8-15-95 20 y M w/Ethanol (beverage) C4,1 C9,1 N1,1 N3,1 S9,1
Susp Suicide 10-10-95 14 y F Only Cyclobenzaprine N3,1
Susp Suicide 4-8-95 23 y M w/Ethanol (beverage) N1,3 N3,3 O10,3 S9,3
Susp Suicide 3-5-95 20 y F w/Ethanol (beverage) C4,1 C8,3 C9,1 N3,1 N7,1 N11,1 O7,1 R4,1 M18,1
Susp Suicide 7-22-95 UA y F w/Ethanol (beverage) N3,1
Susp Suicide 10-4-95 29 y F w/Ethanol (beverage) C9,1 M18,1
Susp Suicide 9-4-95 13 y F Only Cyclobenzaprine N3,1 S9,1
Susp Suicide 10-5-95 21 y M w/Diphenhydramine (OTC) C8,1 C9,1 N17,1

Death:

Susp Suicide 7-17-95 55 y F w/Calcium antagonists C1,1 C2,1 C5,1 C6,1 C7,1 S8,1
Susp Suicide 12-27-95 42 y F w/Amitriptyline C2,1 S8,1
Susp Suicide 8-15-95 42 y M w/Amitriptyline C2,1 C4,1 G12,1 N3,1 M1,1 M8,1
Susp Suicide 5-7-95 35 y F w/Ibuprofen (OTC) C9,1 N7,1 N20,1 C2,1

1996 Medical Outcome:

Moderate Effects:

Abuse 1-17-96 42 y F w/APAP: adult formul. C9,1 D3,1 H1,1 N4,1 N20,1 M16,1
Abuse 3-26-96 31 y M w/Benzodiazepines C8,2 C9,1 G12,1 N2,3 N4,3 N7,3 N10,3
Abuse 12-14-96 26 y M w/Ethanol (beverage) N1,1 N7,1 M18,1
Int Misuse 8-20-96 28 y M w/Ibuprofen-OTC G16,1 N2,1 N7,1 N11,1
Int Misuse 4-29-96 UA y F w/ethanol (beverage) N4,1
Abuse 1-5-96 32 y M w/Phenothiazines N8,1
Abuse 2-18-96 33 y F w/ APAP w Codeine N7,1 N10,1
Abuse 9-5-96 17 y F w/Oil Base Paint (Inhal) C9,3

Not followed, judged nontoxic: None

Not followed, minimal effects possible:

Abuse 11-14-96 26 y F w/Cocaine N1,1 N15,2 N7,1
Abuse 4-10-96 37 y M w/APAP w Propoxyphene N1,1 N4,1 N7,1 N20,1
Int Misuse 8-24-96 18 y F w/Ethanol (Beverage)
Acc Misuse 2-25-96 24 y F w/Ethanol (Beverage)
Abuse 3-9-96 30 y M w/Other NSAID
Abuse 2-26-96 16 y M w/Phenothiazines D6,3 G12,1 N6,3 N7,3
Abuse 3-12-96 22 y F w/Other skeletal muscle relaxant
Int Unknown 2-24-96 17 y M w/Ethanol (beverage)
Abuse 6-25-96 47 y F w/Ethanol (Beverage) N7,1
Abuse 11-6-96 35 y M w/Hallucinogenic Mushrooms N1,1 N4,1 N7,1
Abuse 11-12-96 15 y M w/Ethanol (beverage)
Abuse 6-26-96 28 y M w/ethanol (beverage) N7,1
Abuse 3-3-96 32 y F w/Other Skeletal Muscle Relaxant N 7,1 N20,1
Abuse 5-4-96 33 y M w/Ethanol (Beverage)

Unable to follow, potentially toxic:

Abuse 2-15-96 42 y F w/APAP & Propoxyphene
Abuse 3-17-96 22 y M w/Ethanol (beverage) N2,1 N7,1
Abuse 10-10-96 17 y M w/Ethanol (beverage) M18,1
Abuse 11-2-96 30 y F w/APAP& Codeine (Cyclobenz parenteral)
Abuse 10-23-96 UA y F w/Benzodiazepines N7,1
Abuse 2-21-96 40 y M w/Ethanol (beverage)

Abuse 11-23-96 32 y M w/Ethanol (beverage) N2,1 N7,1 N11,1 N20, 1
Abuse 2-13-96 35 y F w/APAP other Narcotic G12,1 N6,1 N7,1 N10,1
Abuse 32 y F 10-28-96 w/Ethanol (Beverage)
Abuse 9-10-96 19 y M w/Cocaine (Inhal)
Abuse 12-3-96 32 y M w/Ethanol (beverage)

Major effect:

Susp Suicide 1-28-96 26 y M w/Cocaine (Inhal/Nas) C4,1 C9,1 N3,1 N19,1 S10,1 M13,2 M18,3
Susp Suicide 9-1-96 43 y M w/ethanol (beverage)C8,1G7,1H8,1 N3,1 N10,1 N23,1 M2,1
Susp Suicide 12-19-96 36 y M w/Ethanol (beverage) N1,1 N3,1 N7,1 S9,1
Susp Suicide 2-19-96 20 y M w/Ethanol (beverage) S9,1
Susp Suicide 3-15-96 35 y F w/Ethanol (beverage) N3,1
Int Misuse 3-21-96 39 y M w/APAP w/Oxycodone N7,1 N21,1 O6,1
Abuse 3-29-96 3-29-96 30 y M w/APAP/codeine D7,1D14,1N1,1N3,1N4,1M17,1 M18,1
Int Misuse 8-18-96 31 y M w/Cocaine (Inhal/Nas) C1,1 C5,1 N3,3 N5,3
Susp Suicide 8-10-96 39 y F w/Ethanol (beverage) C9,1 N3,1 O7,1 S9,1
Susp Suicide 6-15-96 28 y M w/Ethanol (beverage) N1,1 N3,1
Susp Suicide 1-18-96 35 y F w/Ethanol (beverage) C9,1 N1,1 N7,1 S9,1
Susp Suicide 4-25-96 13 y F Only Cyclobenzaprine C8,3 C9,1 N3,1 N7,1 O7,1
Susp Suicide 2-4-96 13 y F w/Amitriptyline C7,1 N1,1 S9,1 M1,1
Susp Suicide 9-10-96 15 y Fw/AmitriptylineC9,1N3,1O10,1S9,1S10,1M1,1M10,1M13,1
Susp Suicide 12-13-96 42 y M w/Ethanol (beverage) C4,3 C8,3 N1,1 N2,1 N4,1 N7,1
Susp Suicide 2-7-96 18 y M w/Other Skeletal Muscle Relaxant C9,1 N1,1 S8,3
Susp Suicide 11-24-96 23 y F w/Ethanol (beverage) C9,1 N1,1 N7,1 S9,1
Susp Suicide 4-21-96 31 y M w/Ethanol (beverage) C1,2 N1,1 N3,1 S9,1
Susp Suicide 8-11-96 39 y M w/Ethanol (beverage) C9,1 N3,1
Susp Suicide 8-14-96 15 y F Only Cyclobenzaprine N3,1 N7,1

Deaths:

Abuse 1-30-96 28 y M w/Ethanol C2,1 S7,1 S8,1
Susp Suicide 5-16-96 35 y F w/misc. Rx/OTC C2,3 C4,3 C6,3 C7,3 N17,1 N3,1 O10,1
Abuse 8-27-96 27 y M w/ Cocaine C2,1 C4,3 C7,3 N3,3 S3,3 S9,3 C5,1 O7,1
Susp Suicide 7-24-96 32 y F w/Amitriptyline C2,1 C4,1 C5,1 C6,1 N18,1 R4,1
Susp Suicide 5-6-96 34 y M w/Propoxyphene C1,1 C2,1 N3,1 N17,1 S8,1

1997 Medical Outcome:

Moderate Effects:

Abuse 6-17-97 30s M w/Ethanol (beverage) C9,1 N7,1
Int Misuse 6-9-97 18 y M w/Marijuana N1,1 N4,1 N7,1 N10,1
Abuse 7-22-97 21 y M w/Ethanol (beverage) N2,1
Abuse 2-8-97 19 y M w/Ethanol (Beverage) N1,1 M18,1
Abuse 9-26-97 21 y M w/Trazodone N7,1 N18,3
Abuse 1-27-97 63 y F W/NSAID N7,1 N20,1 N23,1
Abuse 5-8-97 33 y M w/ethanol (beverage) N6,1 N7,1 N20,1 M18,1
Abuse 11-28-97 18 y F w/Antihistam (excl cough/cold preps) C9,1 N1,1 N7,1 N20,1 M18,1
Abuse 11-19-97 37 y M w/Piperonyl butoxide/Pyrethrins D6,1 N1,1 N10,1
Abuse 10-2-97 45 y F w/Methocarbamol D9,1 N4,1 N10,1 N20,1 M18,1
Abuse 2-7-97 31 y F w/Amitriptyline C9,1 G16,1 N1,1 N7,1 M2,1
Abuse 2-1-97 UA y M w/Benzodiazepines N4,1 N7,1 N20,1

Not followed, judged nontoxic: None

Not followed, minimal effects possible:

Int Misuse 6-3-97 35 y M w/Carisoprodol (alone) N4,1
Abuse 5-12-97 41 y M w/Ibuprofen
Int Misuse 9-23-97 31 y M w/Diphenhydramine –alone C9,1 N6,1
Abuse 6-6-97 28 y F w/ASA N7,1
Int Misuse 1-26-97 21 y F w/Diphenyhydramine –alone
Abuse 2-27-97 17 y F w/Cimetidine & other H2 blockers
Abuse 5-15-97 24 y M w/Ethanol (beverage)
Int Unknown 5-31-97 UA F w/Ethanol (beverage)
Int Misuse 1-11-97 38 y F w/Carisoprodol (alone)
Int Misuse 1-5-97 27 y F w/Ethanol (beverage)
Abuse 1-16-97 16 y M w/ NSAID N7,1
Abuse 6-1-97 23 y M w/Ethanol (beverage)
Int Misuse 9-5-97 26 y M w/ethanol (beverage)
Abuse 3-29-97 38 y M w/ ethanol (beverage)
Abuse 12-9-97 50 y F w/Ethanol (beverage) N7,1 N20,1
Acc Misuse 3-23-97 UA F w/Ethanol (beverage)
Abuse 2-23-97 12m M Bacterial food poisoning
Abuse 3-3-97 20 y F w/Other drug unk G16,1
Abuse 3-3-97 4 y M Organophosphate only (alone)
Acc Misuse 3-9-97 8 y w/Amphetamines
Acc Misuse 3-10-97 33 y w/Diphenhydramine (dermal)
Acc Misuse 3-24-97 7 y M w/Diphenhydramine-alone
Acc Misuse 4-4-97 3 y M w/Antihistamine/Decon/no PPA & Narcotic D7,1
Malicious 4-8-97 18 y M w/Feces Urine (ingestion)
Malicious 4-29-97 40 y F w/Other non-drug substance (Inhal/nas) S2,3 M18,3

Unable to follow, potentially toxic:

Unknown 1-5-97 UA F w/Methadone N4,1
Abuse 6-28-97 U U w/ ACE Inhibitors N7,1
Abuse 7-29-97 27 y M w/ Ethanol (beverage) N7,1
Abuse 12-14-97 50s M. w/Ethanol (beverage) N1,1 N7,1 M18,1
Abuse 10-19-97 U U w/Laxatives N1, 1 N7,1 M18,1
Malicious 12-21-97 23 y F Cyclobenzaprine alone
Abuse 5-8-97 31 y F w/ethanol (beverage)
Abuse 7-15-97 40 y M w/benzodiazepines C1, 1 N7, 1
Int Misuse 1-29-97 25 y M w/APAP with Codeine N7,3
Int Misuse 7-27-97 46 y M w/Ethanol (beverage) N 7,1 O1, 1 M18,1
Abuse 10-16-97 UA M. w/Ethanol (beverage) N7,1
Int Misuse 11-25-97 36 y M w/Ethanol (beverage) N7,1
Cont/Tamper 3-25-97 47 y F cyclobenzaprine alone
Abuse 5-4-97 12 y F w/Carisoprodol (alone)
Abuse 10-11-97 32 y M w/Ethanol (beverage) N1,1 N7,1
Int Unknown 7-16-97 51 y F w/Ethanol (beverage)
Abuse 2-9-97 26 y M w/Ethanol (beverage) N2,1 N7,1
Abuse 11-9-97 17 y M w/Antihistamine/decon/no PPA/DM
Int Misuse 12-29-97 20 y M W/ SSRIs N4,1 N7,1
Acc Misuse 3-4-97 34 y M w/ Sleep aids-OTC (not DPH)
Abuse 6-10-97 41 y F w/APAP with propoxyphene
Int Misuse 3-15-97 22 y F w/ SSRIs N6,1
Abuse 8-20-97 48 y F w/Benzodiazepines
Malicious 9-3-97 44 y F w/other nondrug subst.(inhal/Nas) C3,2 G1,3 G5,3 N7,3 N16,3
Abuse 11-3-97 22 y M w/Cocaine C9,1 G16,1 N10,1

Unrelated:

Abuse 9-5-97 52 y M w/Cocaine C8,3 G3,3 N3,2 N5,2

Abuse 8-5-97 68 y M w/Carisoprodol (alone) N23,2 S5,2

Major Effect:

Susp Suicide 2-14-97 27 y F w/Ethanol (beverage) C5,1 N1,1 N3,1 N7,1 M18,1
Susp Suicide 12-26-97 34 y M w/Ethanol (beverage) C8,1C9,1N2,1N3,1N7,1 N20,1S9,1
Susp Suicide 2-16-97 38 y F w/Ethanol (beverage) C9,3 N5,1 N7,1
Unknown 5-24-97 40 y M w/APAP & Narcotic G16,1 N3,1 M1,1 M4,1
Int Misuse 8-8-97 26 y M w/APAP H1,1 H7,1 H8,1 H9,1 N2,1 O7,1 O10,1
Acc General 4-25-97 UA y M w/Ethanol (Beverage) N3,1 N7,1 S9,1
Susp Suicide 4-21-97 17 y M Only Cyclobenzaprine C9,1 N1,1 N4,1 N10,1
Susp Suicide 8-20-97 17 y M w/APAP & codeine N1,1 S9,1 M1,1 M4,1
Susp Suicide 3-4-97 39 y F w/Ethanol (beverage) N3,1 N7,1 S9,1
Susp Suicide 10-20-97 45 y F w/Ethanol (beverage) C8,3 C9,1 N1,1 N3,1 N7,1 S9,1
Susp Suicide 10-23-97 30 y M w/Ethanol (beverage) N7,1 S8,1
Susp Suicide 5-1-97 44 y F w/Ethanol (beverage) N3,1 N7,1 O10,1
Susp Suicide 4-6-97 25 y M w/Ethanol (beverage) N7,1 S9,1 M1,1
Susp Suicide 6-30-97 37 y F w/Ethanol (beverage) C7,1 C8,1 C9,1 N7,1 S9,1
Susp Suicide 6-22-97 25 y M w/Ethanol (beverage) N1,1 N3,1
Susp Suicide 6-27-97 17 y M w/Other Sed/Hyp/Antianx/Antipsychotic C9,1 N3,1 O7,1
Susp Suicide 12-15-97 30 y F w/Ethanol (beverage) C4,1 C9,1 N3,1 N17,1 O6,1
Susp Suicide 12-31-97 35 y M w/Ethanol (beverage) C9,1 N3,1
Int Unknown 2-20-97 15 y F w/Benzodiazepines C9,3 N7,3
Abuse 8-1-97 17 y M w/Ethanol (beverage) C4,1 C9,1 N1,1 N17,1 O7,1
Susp Suicide 11-18-97 36 y F w/Ethanol (beverage) C4,1 C9,1 N1,1 N17,1 O17,1

Death:

Susp Suicide 1-15-97 27 y M w/Antiarrhythmics (Quinidine, Bretylium, Procainamide, etc.) C2,1 C7,1 C9,1 N3,1 S8,1
Unknown 9-8-97 77 y F w/Benzodiazepines C2,3 C5,1 N3,1 M10,1 C1,1 R1,1 M1,1
Susp Suicide 12-19-97 47 y F w/APAP/Codeine C7,1 C9,1 G16,1 H2,1 H3,1 N4,1 N7,1 C2,1 C7,1
Susp Suicide 7-26-97 48 y F w/APAP & Oxycodone N3,1 R1,1 R6,1 C2,1 C7,1
Int Unknown 10-15-97 41 y M w/Benzodiazepines C2,1 C5,1 N3,1 N18,1

CODE: Between 1993 and 1997, clinical effects are coded by their group letter and a symptom number, followed by an indicator of whether the symptom is related (1 = related, 2 = not related, 3 = unknown if related):

Cardiovascular (C)

C1	Bradycardia
C2	Cardiac arrest
C3	Chest pain
C4	Conduction disturbance
C5	Dysrhythmia (other)
C6	Dysrhythmia (v tach v fib)
C7	Hypotension
C8	Hypertension
C9	Tachycardia

Respiratory (S)

S2	Cough/choke
S5	Hyperventilation/tachypnea
S6	Pneumonitis
S7	Pulmonary edema
S8	Respiratory arrest
S9	Respiratory depression
S10	X-ray findings (+)

Renal (GU)

R1	Increased creatinine
R4	Oliguria/anuria
R6	Renal failure
R7	Urinary incontinence
R8	Urinary retention

Heme/Hepatic (H)

H1	AST and/or ALT>100≤1,000
H2	AST and/or ALT > 1,000
H3	Increased bilirubin
H7	PT prolonged
H8	Other coagulopathy
H9	Other LFT abnormality

Dermal (D)

D3	Burns (2nd and 3rd degree)
D6	Edema
D7	Erythema/flushed
D9	Irritation/pain
D13	Puncture wound/sting
D14	Rash

Neurological (N)

N1	Agitation/irritable
N2	Ataxia
N3	Coma
N4	Confusion
N5	CVA
N6	Dizziness/vertigo
N7	Drowsiness/lethargy
N8	Dystonia
N10	Hallucinations/Delusions
N11	Headache
N15	Paralysis
N16	Peripheral neuropathy
N17	Seizure (single)
N18	Seizures (multiple/discrete)
N19	Seizures (status)
N20	Slurred Speech
N21	Syncope
S23	Tremor

Gastrointestinal (G)

G1	Abdominal pain
G3	Constipation
G5	Diarrhea
G7	Esophageal injury
G12	Nausea
G16	Vomiting

Ocular (O)

O1	Blurred vision
O6	Miosis
O7	Mydriasis
O8	Nystagmus
O10	Papilledema
O11	Visual effect

Miscellaneous (M)

M1	Acidosis	M11	Hyperglycemia
M2	ADR to treatment	M12	Hypoglycemia
M3	Alkalosis	M13	Hypothermia
M4	Anion gap increase	M16	Pain
M7	Diaphoresis	M17	Rhabdomyolysis
M8	Electrolyte abnormality	M18	Other
M10	Fever/hyperthermia		